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GROWTH HORMONE AND AGING

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Introduction

Growth hormone (GH) is a peptide containing 191 aminoacids that is secreted by the acidophilic cells of the pituitary and has a very important action on growth during infancy and adolescence (Devesa et al 1996). To perform this action GH needs the collaboration of a full series of factors such as, thyroid hormones and sexual hormones together with an appropriate nutrition.

GH is under the hypothalamic control of two peptides, one stimulating, GHRH firstly discovered in 1982 (Guillemin et al 1982, Rivier et al 1982), and another inhibitory, somatostatin, that is a tetradecapeptide, discovered in 1973 by Brazeau et al (1973).

Interaction between GHRH and somatostatin plays a significant role in the secretion of GH and somatostatin seems to play the major role (Devesa and Tresguerres 1996). GHRH is secreted in peaks as well as somatostatin, both with 180° shift, so that the GH peak appears when GHRH levels are high, and somatostatin levels are low. GH disappears from blood when somatostatin values are high in the hypothalamus and GHRH is low (Tanenbaum and Link 1983). This control is exerted so that GH is secreted every 3h. approximately, with higher amplitude during the night, actually during slow wave sleep. Some of the actions of GH are exerted through an intermediary product, IGFI, that it is synthesized in the liver and in other tissues under the stimulation of GH (Tresguerres 1996)

IGFI is a peptide of 70 aminoacids that shows similarities with proinsulin and acts on a paracrine way on the growth plates of the long bones stimulating the multiplication of chondrocytes and determining growth. IGF I generated in the liver under GH stimulation circulates in the blood bound to a series of transport proteins called IGF BPS that are also GH dependent, especially IGFBP 3. However the most important role is exerted by this a peptide, when synthesized locally in a paracrine way (Tresguerres 1996).

Aging as a model of GH deficiency.

GH stimulates growth when given to children or adolescents as substitution therapy to treat is deficiency so that children are capable of reaching a normal stature if treated conveniently and starting from a very young age (Casado de Frias et al 1996). The therapeutical use with GH started in 1957 (Raven et al 1957) and from that time on an evident beneficial action of GH therapy has been obtained in those patients. However when those children reached puberty and the growth plates became closed, GH therapy was discontinued since it was considered as not playing afterwards any significant role in the body.

However when a very broad study was performed some years ago, investigating the evolution in the adult age of those patients that were treated as children with GH, a significant number of problems were detected that included an abnormal composition of the body, with increase in central fat and muscular weakness with a reduction in bone density, fatigue and reduction of the subjective sensation of well being (Sassolas 1994). In addition an increase in cardiovascular mortality, has been detected (Rosen and Bengtsson 1990, Bates et al 1996). All this facts make evident that GH is also important in a full series of vital functions in our body also after final height has been achieved.

The aging process in man is associated with a reduction in muscular and bone mass together with an increase in body fat (Forbes 1976). Aged people show very reduced GH and GFI values in plasma as compared to young individuals (Toogoot, and Colls 1996), so that the observed metabolic changes have been correlated with body composition and the reduction of GH and IGFI levels, starting to speak about the existence of a true "somatopause" (Hoffman et al 1993). All these processes are evident after sixty years of age, so that aging itself could be considered as a form of "GH deficiency". Old people show muscular atrophy, an increase in central fat together with osteoporosis and a reduction in the immunological competence, so that neoplastic processes are favoured (Iglesias et al 1996). All

these changes can be influenced by the exogenous administration of GH, since the substitution therapy with this hormone stimulates muscular development, induces loss of fat tissue and enhances bone density (De Boer et al 1995, Gibney et al 1999).

The mechanisms that could play a role in the reduction of the GH associated with age have been thoroughly investigated and the following ethyologies are possible: 1) Reduction in hypothalamic GHRH, 2) An Increase in somatostatin secretion, 3) Reduction in the number of somatotrophic cells in the pituitary, 4) Increase the sensitivity to the negative feed back of IGFI.

The majority of papers agree that the principal alterations during somatopause should be located in the hypothalamus. A reduction in GHRH secretion (Ono et al 1986, De Gennaro Colonna et al 1989) and/or an increase in somatostatinergic activity (Locatelli et al 1984) seem to be responsible for the appearance of very low plasma GH levels during aging.

Another important fact that needs to be taken in to account is, that GH secretion is dependent of slow wave sleep (Van Cauter and Plat 1996). During aging a reduction in this type of sleep has been detected. This is probably motivated by a reduction of the nocturnal melatonin secretion (Copinschy y Van Cauter 1995), that could play also a role in GH diminution.

Substitution therapy of GH deficiency during aging.

Since the important work performed by Rudman et al (1990), it has been demonstrated that treatment with GH, in old people can exert a very positive role in the reduction of hormonal and metabolic changes associated with aging. GH administration to men older than sixty years of age is capable of restoring IGF I levels to approximately those appearing in young persons including an increase in muscular mass, bone density and the reduction in the percentage of body fat (Rudman et al 1990, Holloway et al 1994, Cuttica et al 1997). Adverse side effects can appear if the treatment is prolonged and high dosages of GH are used, but always those secondary effects are of minor entity. When low doses of GH were used for a period of 10 years of treatment side effects were nearly absent (Gibney et al 1999).

Experimental studies have been performed in rats, that were treated over small periods of time, always lower than fifteen days, showing the same positive effects observed in men (Cartee et al

1996): increases in muscular mass and in heart weight (De Gennaro, Colonna y Colls 1993).

Effects on muscular system

Physiological aging shows a reduction in lean body mass with an increase in body fat that is associated with a reduction in the capacity to perform exercise and also leads to cardiovascular alterations especially by the existence of hyperlipidemia (Rosen and Bengtsson 1990).

These changes are similar to those appearing during GH deficiency (Rosen et al 1993). In all those cases treatment with the biologic synthetic GH increases basal metabolism (Van Wyck et al 1988) with the establishment of a positive nitrogen balance (Valk et al 1994) due to an enhancement of aminoacid absorption in the digestive system (Copeland and Nair 1994). This also stimulates protein synthesis and leads to an increase in muscular mass (Juul 1996), in physical strength (Jorgensen et al 1991) and to the normalization of lean body mass (Salomon et al 1989).

Effects on the cardiovascular system

GH has been shown to increase cardiac function (Amato et al 1993), increasing left ventricular mass and left ventricular output (Valcavi et al 1995). As a consequence, there is an increase in the capacity to perform exercise with an increase in oxygen consume (Nass et al 1995). Carotid intima thickness was also reduced (Gibney et al 1999).

GH administration reduces cholesterol levels (Weaver et al 1995), redistributing and reducing body fat and this leading to a reduction in cardiovascular risk.

Substitution therapy with GH has a beneficial effect inducing a lipolytic action on the adipocytes and establishing a better relationship HDL / LDL cholesterol (Beshyah et al 1995 and Angelopoulos et al 1998). All these effects are maintained also when the treatment is maintained for long periods of time. Jorgensen et al (1994) have shown patients treated for more than three years without the appearance of important secondary effects and Gibney et al (1999) for more than 10 years so that recently the treatment of the dilated cardiomyopathy with GH has been proposed (Osterziel et al 1998) as well as other cardiac diseases.

Actions on the bone

One of the problems that has direct incidence on the quality of life of aged patients is the reduction of bone mass. This problem is more evident in the woman and can be, at least partially

prevented in those, with the substitution therapy with sexual hormones after menopause. The reduction in bone mass can very markedly limit motility and can also generate pathologies that are potentially very serious, like hip fractures and vertebral crushing (Iglesias et al 1996).

GH administration increases calcium, phosphate and osteocalcin levels in plasma. Under GH deficiency there is a reduction in mineral bone density (Dagerblad et al 1995) similar to what happens during aging. Treatment with GH is capable of increasing bone turnover. Thus the rationale for treatment of bone problems with GH seems logical. In the case of women, this treatment can be associated with sexual steroids (Holloway et al 1994), potentiating the beneficial effects of those. In experimental studies GH increases Calcium absorption in old rats and both GH, IGF I are capable of stimulating directly the osteoblastic activity (Kassem et al 1993), so GH treatment is capable of increasing bone mass in patients with GH deficiency (O'Halloran et al 1993).

Experimental studies

Experimental studies performed in our laboratory, using aged rats showed that the daily administration of GH to animals of 24 months of age elicited beneficial effects in the same way as those seen in humans. Animals treated during one month with 2 UI of GH subcutaneously twice a day showed an increase in muscular mass, with an increase in lean body mass, and a reduction of body fat. IGFI levels were increased as well as osteocalcin whereas alkaline phosphate was reduced. Blood cholesterol was not modified but free fatty acids were increased as a result of lipolysis.

Effects on the quality of life

Hypopituitarism is associated with higher cardiovascular mortality (Rosen and Bengtson 1990, Bates et al 1996). In the old population, higher cholesterol and triglyceride levels are present, with an increase in central body fat, that is related to cardiovascular risk. Substitution therapy with GH leads to a significant reduction of those parameters (Rosen et al 1993, Gibney et al 1999), together with an increase in physical capacity (Jorgensen et al 1991) and a better cardiac performance (Amato et al 1993). This is associated with an increase in the sense of well being.

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REFERENCES

1. Amato G, Carella C, Fazio S, La Montagna G, Cittadini A, Sabini D, Maricano-Mome C, Sacca L, Bellstela A.
Body composition, Bone metabolism and heart structure and function in GH deficient adults before and after GH replacement therapy at low doses.
J Clin Endocrinol Metab, 77:1671-1676 (1993).
2. Angelopoulos TJ, Seip RL, Cole TG.
Effect of short term recombinant GH administration on plasma lipoproteins in elderly adults.
Gerontology 44:228-231 (1998).
3. Bates AS, Van't Hoff W, Jones PJ, Clayton RN
The effect of hypopituitarism on Life Expectancy
J. Clin. Endocrinol Metab. 81: 1169 - 1172 (1996)
4. Beshyah SA, Henderson A, Nithyananthan R, Skinner E, Anyaku V, Richmond W, Sharp P, Johnston DG.
The effects of short and long term GH replacement therapy in hypopituitary adults on lipid metabolism and carbohydrate tolerance.
J Clin Endocrinol Metab, 80:356-363 (1995).
5. Brazeau P, Vale W, Burgus R, Ling N, Bitcher M, Rivier J, Guillemin R.
Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone.
Science, 179:77 (1973).
6. Cartee GD, Bohn EE, Gibson BT, Farrar RP.
Growth hormone supplementation increases skeletal muscle mass of old male Fisher 344/brown Norway rats.
J. Gerontol 51:B219-214 (1996).
7. Casado de Frías E, Bueno G, Ruibal JL.
Tratamiento de los déficits de GH en (Moreno y Tresguerres dir)
"Retrasos de crecimiento" 2ª Ed., Díaz de Santos. Madrid. pp 365-376 (1996).
8. Copeland KC, Nair KS
Acute GH effects on aminoacid and lipid metabolism.
J. Clin Endocrinol Metab. 78:1040-47 (1994).
9. Copinschi G, Van Cauter E.
Effects of ageing on modulation of hormonal secretion by sleep and Circadian Rhythmicity.
Horm Res 43:20-24 (1995).

10. Cuttica CM, Castoldi L, Gorrini GP, Peluffo F, Delitala G, Filippa P, Fanciulli G, Giusti M. Effects of six-month administration of rhGH to healthy elderly subjects. *Aging* 9: 193-197 (1997).
11. De Boer H, Block GJ, Van Der Veen EA. Clinical aspects of growth hormone deficiency in adults. *Endocr Rev* 16: 63-68 (1995).
12. De Gennaro Colonna V, Zoli M, Cocchi D, Maggi A, Marrama P, Agnati LF, Müller EE. Reduced growth hormone releasing factor (GHRH)-like immunoreactivity and GHRF gene expression in the hypothalamus of aged rats. *Peptides* 10:705-708 (1989).
13. Degerblad M, Bengtsson BA, Brannert M, Johnell O, Manhem P, Rosen T, Thoren M. Reduced bone mineral density in adults with GH deficiency: Increase bone turnover during 12 months of GH substitution therapy. *Eur J Endocrinol*, 133:180-188 (1995).
Devesa J, García M, Costoya JA, Gondar M, Gavrilina J, Gavrilin M y Arce V. Expresión de los genes de GH, variantes moleculares y acciones biológicas de estas variantes en (Moreno y Tresguerres dir). "Retrasos de crecimiento" 2ª Ed., Díaz de Santos. Madrid. pp 29-44 (1996).
14. Devesa J, Tresguerres JAF. Control de la secreción de GH en (Moreno y Tresguerres dir). "Retrasos de crecimiento" 2ª Ed., Díaz de Santos. Madrid. pp 45-60 (1996).
15. Forbes G. The adult decline in lean body mass. *Human Biol* 48:161-173 (1976).
16. Gibney J, Wallace JD, Spinks T, Silhorr L, Ranicar A, Cuneo RC, Lockhart S, Burnand KG, Salomon F, Sonksen PH, Russel - Jones D. The effects of 10 years of recombinant GH in adult GH deficient patients. *J. Clin. Endocrinol Metab.* 84: 2569-2602 (1999).
17. Guillemin R, Brazeau P, Bohlen P, Esch F, Ling N, Wherenberg WB. GH releasing factor from a human pancreatic tumor that caused acromegaly. *Science*, 216:585 (1982).
18. Hoffman AR, Pyka G, Lieberman SA, Ceda GP, Marcus R. The somatopause. En Müller EE, Cocchi D, Locatelli V (eds.): "Growth hormone and somatomedins during lifespan". Springer Berlin, 265-274 (1993).
19. Holloway L, Butterfield G, Hintz RL, Gesundheit N, Marcus R. Effects of recombinant hGH on metabolic indices, body composition and bone turnover in healthy elderly women. *J Clin Endocrinol Metab*, 79:470-479 (1994).
20. Iglesias P, Díez JJ, Gómez-Pan A. Empleo terapéutico de la GH en adultos en (Moreno y Tresguerres dir). "Retrasos de crecimiento" 2ª Ed., Díaz de Santos. Madrid. pp 377-396 (1996).
21. Jorgensen JOL. Human growth hormone replacement therapy: pharmacological and clinical aspect. *Endocr. Rev.* 12: 189-207 (1991).
22. Jorgensen JOL, Pedersen SA, Thuesen L, Jorgensen J, Moller J, Müller J, Skakkeback EN, Christiansen JS. Long term GH treatment in GH deficient adults. *Acta Endocrinol*, 125:449-453 (1991).
23. Jorgensen JOL, Thuesen L, Müller J, Ovesen P, Skakkeback, Christiansen JS. Three years of GH treatment in GH deficient adults: near normalization of body composition and physical performance. *Eur J Endocrinol*, 130:224-228 (1994).
24. Juul A. Adult GH deficiency and effect of GH treatment on muscle strength, cardiac function and exercise performance in Juul A and Jorgensen JOL, (eds) "GH in adults". Cambridge. Univ press 1996 pp234-245.
25. Kassem M, Blum W, Ristelli J, Mosekilde L, Eriksson EF. GH stimulates the proliferation and differentiation of normal osteoblast like cells in vitro. *Calcif Tissue Int*, 52:222-226 (1993).
26. Locatelli V, Arimura A, Torsello A, Cella SG, Müller EE. Somatostatin antiserum antagonizes the impaired ability of hpGRF-40 to stimulate growth hormone release in old unanesthetized male rats. *Neuroendocrinol Lett* 6 : 261-265 (1984).
27. Nass R, Huber RM, Klauss V, Müller OA, Schopohl J, Strasburger CJ. Effect of hGH replacement therapy on physical work capacity and cardiac and pulmonary function in patients with hGH deficiency acquired in adulthood.

J Clin Endocrinol Metab, 80:552-557 (1995).

28. O'Halloran DJ, Wieringa G, Tsatsuolis A, Shalet SM.

Increased serum lipoprotein (a) concentrations after GH treatment in patients with isolated GH deficiency.

Ann Clin. Biochem 33:330-334 (1996).

29. Ono M, Miki N, Shizume K.

Release of immunoreactive growth hormone-releasing factor (GRF) and somatostatin from incubated hypothalamus in young and old male rats (Abstract).

Nueroendocrinology 43 (suppl) : 111 (1986).

30. Osterziel KJ, Strohm O, Schuler J, Friedrich M, Haenlein D, Willenbrock R, Anker SD, Poole-Wilson, Ranke MB, Dietz R.

Randomised, double-blind, placebo-controlled trial of human recombinant GH in patients with chronic heart failure due to dilated cardiomyopathy.

Lancet 351:1233-7 (1998).

31. Raben MS

Preparation of GH from pituitaries of men and monkey.

Science 125:883- (1957).

32. Rivier J, Spiess J, Thorner M, Vale W.

Characterization of a GH releasing factor from a human pancreatic islet tumor.

Nature, 300:276 (1982).

33. Rosen T, Bengtsson BA.

Premature mortality due to cardiovascular disease in hypopituitarism.

Lancet, 336:285-288 (1990).

34. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE.

Effects of human GH in men over 60 years old.

N Engl J Med, 323:I-6 (1990).

35. Salomon F, Cuneo RC, Hesp R, Sönksen PH.

The effects of treatment with recombinant human GH on body composition and metabolism in adults with GH deficiency.

N Engl J Med, 321:1797-1803 (1989).

36. Sassolas G.

Potential therapeutic application of GH in adults.

Horm Res, 42:72-78 (1994).

37. Tannenbaum GS, Ling N

The interrelationship of GH RH and somatostatin in generation of the ultradian rhythm of GH secretion.

Endocrinology 115:1952 - (1984)

38. Toogood AA, O'Neill PA, Shalet SM.

Beyond the somatopause: GH deficiency in adults over the age of 60 years.

J Clin Endocrinol Metab, 81:460-465 (1996).

39. Tresguerres JAF.

Somatomedinas (IGFs) y sus proteínas transportadoras en (Moreno y Tresguerres dir).

"Retrasos del crecimiento" 2ª Ed., Díaz de Santos. Madrid. pp 61-72 (1996).

40. Valcavi R, Gaddi O, Zini M, Iavicoli M, Mellino U, Portioli I.

Cardiac performance and mass in adults with hypopituitarism: Effects of one year of GH treatment.

J Clin Endocrinol Metab, 80:659-666 (1995).

41. Valk NK, Lely AJ, Herder WW, Lindemans J, Lamberts SWJ.

The effect of GH administration on GH-deficient adults: A20 day metabolic ward study..

J. Clin Endocrinol Metab. 79: 1070-76 (1994).

42. Van Cauter E and Plat L.

Physiology of GH secretion during sleep

The Journal of Pediatrics 128:532-537 (1996).

43. Van Wyk JJ, Casella SJ, Hynes M, Lund PK.

Indirect actions of GH en (Underwood LE ed.)

"Human Growth hormone Progress and challenges". Marcel Dekker, New York, Basel. pp 25-61 (1988).

44. Weaver JU, Monson JP, Noonan WG, Edwards JA, Evans KA, Cunningham J.

The effect of low dose recombinant hGH replacement on regional fat distribution, insulin sensitivity and cardiovascular risk factors in hypopituitary adults.

J Clin Endocrinol Metab, 80:153-159 (1995).